Vaccination and occult hepatitis

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MUH

Vaccination

- Vaccination is a method of giving antigen to stimulate the immune response through active immunization.

- A vaccine is an immuno-biological substance designed to produce specific protection against a given disease.
- A vaccine is “antigenic” but not “pathogenic”.

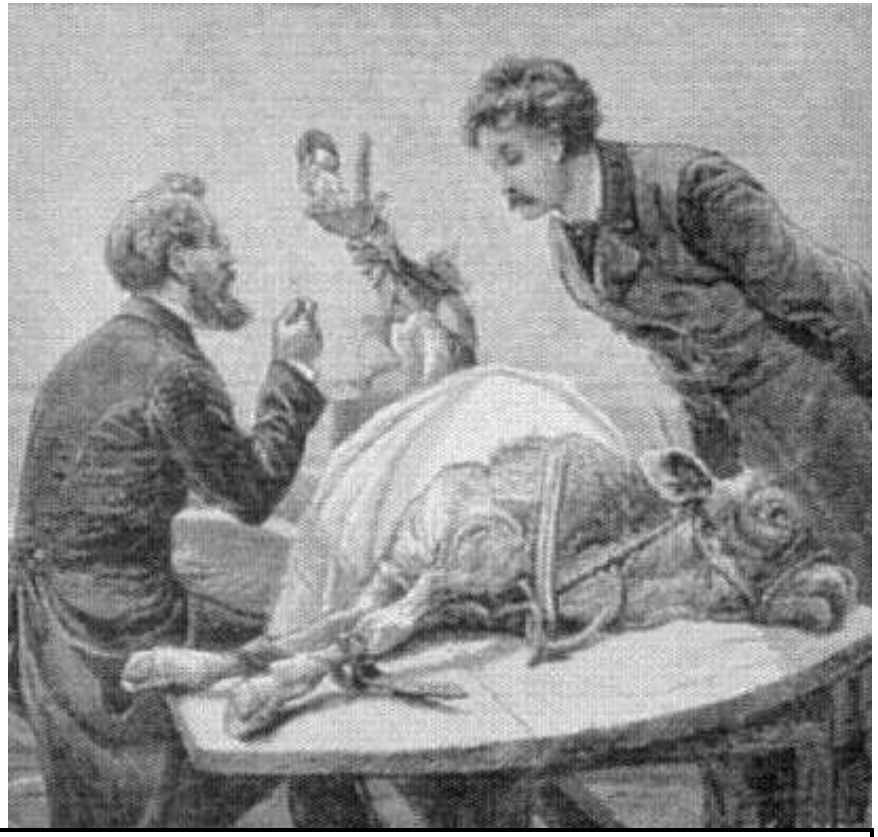
Milestones in immunization

- 3000BC
  - Evidence of sniffing powdered small pox crust in Egypt
- 2000BC
  - Sniffing of small pox crust in China
- 1500BC
  - Turks introduce variolation
- 1700AD
  - Introduction of variolation in England and later in the US

Vaccines-Historical Perspective

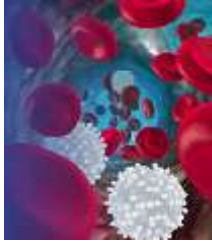
- ***7th century***- Indian Buddhists' drank snake venom to protect against snake bite.
- ***10th century***- Variolation to prevent smallpox in China and Turkey.
- ***Early 1700s***- Variolation introduced into England.
- ***1760-70- The Jennerian era.***
- ***1875-1910***- Dawn of Immunological Science.
- ***1910-30***- Early bacterial vaccines, toxins and toxoids.
- ***1930-50***- Early viral vaccines: yellow fever and Influenza.
- ***1950-1970***- The tissue culture revolution: poliomyelitis, measles, mumps and rubella.
- ***1970-1990***- Dawn of the molecular era: hepatitis B, *Streptococcus pneumonia*, *Hemophilus influenza* B.
- ***Today***- Glycoconjugate vaccines, rotavirus vaccine, human papilloma virus vaccine and herpes zoster vaccine.

Edward Jenner



Discovery of small pox vaccine

What is Vaccinology?



- Vaccinology is the science of developing vaccines to prevent diseases

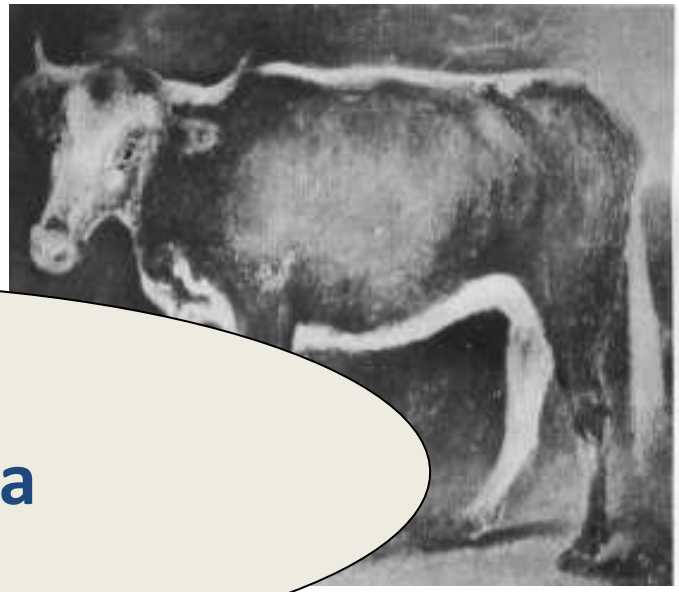
Let’s go back in time to see how this strategy works

- The time: 500 B.C.
- The place: Greece

Even 2,500 Years Ago, People Knew Immunity Worked.

- Greek physicians noticed that people who survived smallpox never got it again.
- The insight: Becoming infected by certain diseases gives immunity.

Fast forward 2300 years



I had a brilliant idea

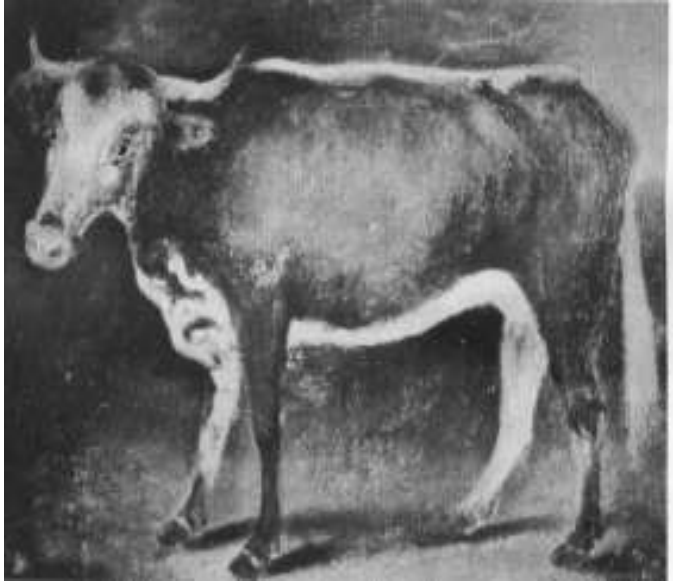
pathmicro.med.sc.edu/ppt-vir/vaccine.ppt

He always takes all the credit!

pathmicro.med.sc.edu/ppt-vir/vaccine.ppt

Vaccination

- Jenner 1796 : Cowpox/Swinepox
- 1800's Compulsory childhood vaccination



Vaccines Achievements[2]

- **"At the end of the 20th century the US Centers for Disease Control and Prevention (CDC) cited vaccination as the number *one* public health achievement of that century"**

- **"The elimination in 1977 of smallpox as a human disease must rank as *one* of the major achievements of modern medicine"**

Types of vaccines

- Live vaccines
- Attenuated live vaccines
- Inactivated (killed vaccines)
- Toxoids
- Polysaccharide and polypeptide (cellular fraction) vaccines
- Surface antigen (recombinant) vaccines.

Viral Vaccines

DISEASE	VIRUS TYPE	CONSTITUENTS	EFFICACY
SMALLPOX	Variola virus	Vaccinia virus	100
POLIO	Picornavirus	Oral: live attenuated Parenteral: inactivated	>95% >95%
HEPATITIS A	Picornavirus	Killed virus	>90%
HEPATITIS B	hepadnavirus	Recombinant antigen	>80%
INFLUENZA	Orthomyxovirus	Inactivated virus	50-70%
MEASLES	Paramyxovirus	Live, attenuated virus	>95%
MUMPS	Paramyxovirus	Live, attenuated virus	>90%
RUBELLA	Togavirus	Live, attenuated virus	>95%
CHIKEN POX	Varicella zoster	Live, attenuated virus	>80%
RABIES	Lyssa virus	Inactivated virus	100
YELLOW FEVER	Flavivirus	Live, attenuated virus	>90%
JAPANESE ENCEPHLITIS	Flavivirus	Inactivated virus	>90%

Bacterial Vaccines

DISEASE	ORGANISM	VACCINE	EFFICACY
DIPHTHERIA	*Corynebacterium diphtheriae*	Inactivated exotoxin	>95%
TETANUS	*Clostridium tetani*	Inactivated exotoxin	>95%
MENINGITIS	*H influenzae* *Neisseria meningitidis*	Polysaccharide protein congugate/ purified polysacc	>90% for <2yrs
PNEUMONIA	*Strep pneumoniae*	Purified polysaccharide Polysac-protein congugate	60% for >2 yrs > 95%
WHOOPING COUGH	*Bordetella pertussis*	Acellular components – incl inactvated toxin, fimbriae	80-90%
PLAGUE	*Yersinia pestis*	Inactivated bacteria	uncertain
ANTHRAX	*Bacillus anthracis*	Inactivated bacteria	uncertain
TUBERCULOSIS	*Mycobacterium tuberculosis*	Live attenuated BCG	Disseminated disease protection
CHOLERA	*Vibrio cholerae*	Inactivated bacteria	50% (short)

Target Fungal Vaccines

DISEASE	ORGANISM	IMMUNITY	VACCINE
HISTO-PLASMOSIS	*Histoplasma capsulatum*	CMI	H glycoprotein, HSP 62, CW, CM
COCCIDIO-MYCOSIS	*Coccidiodis immitis*	CMI	Enzyme, CW, urease, Water sol Ag,
BLASTO-MYCOSIS	*Blastomycis dermatidis*	CMI	W-1 surface adhesin
CRYPTO-COCCOSIS	*Cryptococcus neoformans*	Humoral	Capsular polysaccharide, melanin
CANDIDIASIS	*Candida albicans*	Humoral CMI	Mannan, mannoprotein Enolase
PCP	*Pneumocystis jiroveci*	CMI	Major surface glycoproteins

Target Parasitic Disease

- **Malaria**
- **Trypanosomiasis**
- **Leishmaniasis**
- **Toxoplasmosis**

More Possibilities

- Therapeutic vaccines: Identification of specific tumor antigens provide immune targets for which immunogenic vaccines may conceivably be designed. **Examples**:
  - Leukemia
  - Breast cancer
  - Melanoma
  - Prostate cancer
  - Colon cancer

- Vaccines against autoimmune diseases

Vaccine Safety

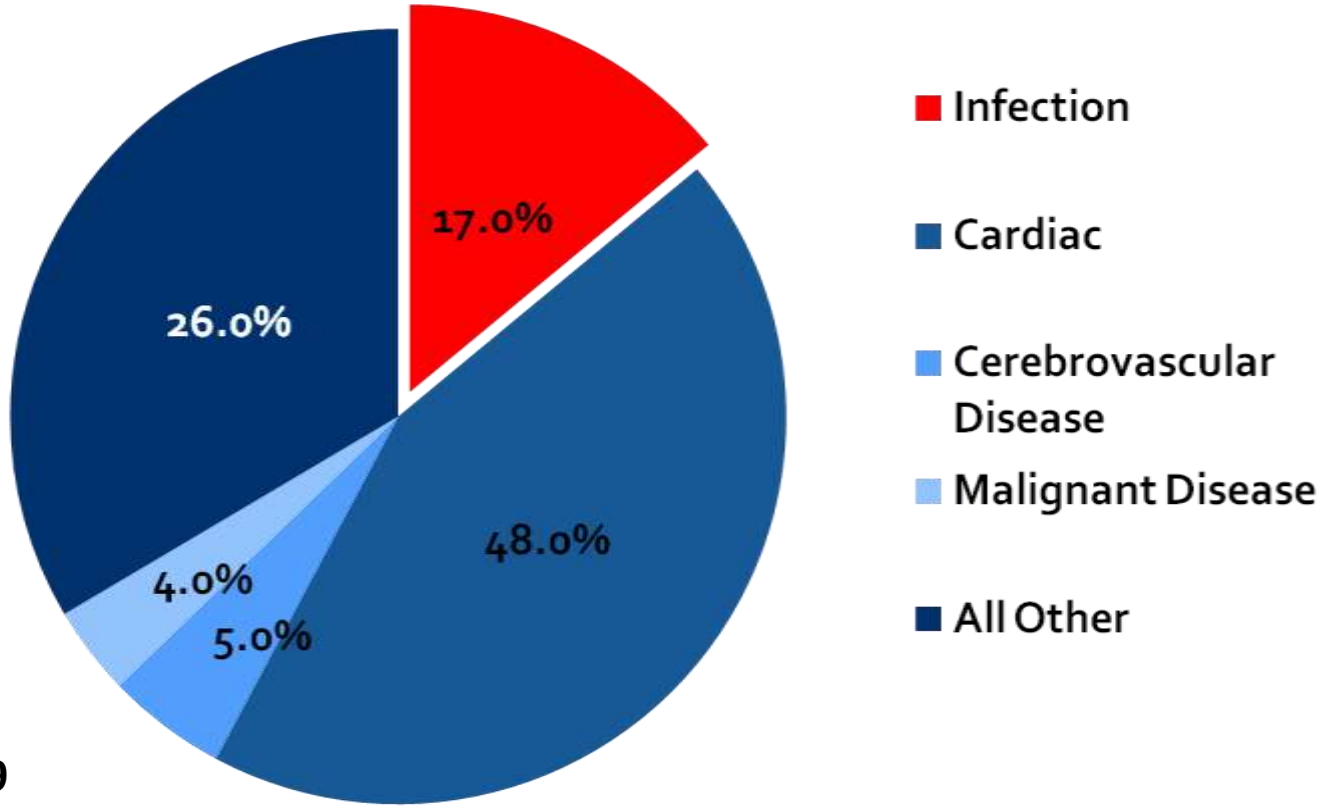
Chronic kidney disease (CKD)

Alteration of the innate and adaptive immunity.

Infection is the 2nd leading cause of death

Naqvi SB, Collins AJ. Infectious complications in chronic kidney disease. Adv Chronic Kidney Dis. 13(3), 199-204, 2006.

Infections: A Major Patient Safety Problem in Dialysis – 2nd Leading Cause Of Death



UM-KECC, 2009

Approximately 15,000 dialysis patients die annually due to infections

How Are Infections Spread in Dialysis?

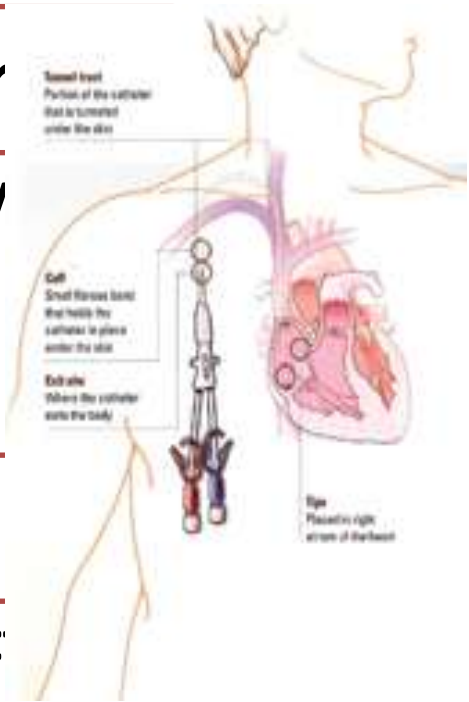
Five potential "routes" of pathogen transmission:

- On the hands of staff going between patients & between common areas and patients
- From ineffectively disinfected equipment & environmental surfaces
- From contaminated supplies & medications

How Are Infections Spread in Dialysis? (cont.)

4. From inadequate vascular access car

- Vascular access is the primary portal for dialy patient infections
- Central Venous Catheters (CVC) have 7 times higher infection rates than AV fistula (AVF)



5. From virulent pathogens

- Hepatitis B virus remains viable and transmit for at least 7 days on surfaces
  - In 1974 6.2% of hemodialysis patients acquired hepatitis B-some facilities had as high as 30% HBV+

Why Hand Hygiene & Surface Disinfection Are Vital

Organisms remain viable on surfaces for prolonged periods

• Hepatitis B	>1 week
• Influenza	1-2 days
• MRSA	7 days to 7 months
• VRE	5 days to 4 months
• C. difficile spore	5 months

Healthcare workers touch as many as 7 surfaces after touching a contaminated one!

McLaughlin AC, Walsh F. Am J Infect Control 39(6):456-463, 2011
Kramer A, Schwebke I, Kampf G. BMC Infect Dis 6:130, 2006

however vaccine efficacy remains far from optimal in the CKD population.

reduced response to vaccination because of the general immune suppression associated with uremia

decreased cellular responses

disturbances in humoral innate immunity e.g. low complement IV factor, decreased cytokine response after stimulation

Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol. 3(5), 1526-1533, 2008

Pneumococcal Polysaccharide Vaccine

A single dose of 0.5 ml of the 23 valent pneumococcal polysaccharide vaccine

intramuscularly or subcutaneously

dialysis patients 2 years of age or older

Revaccination is recommended after 3 years

children with chronic renal disease

10 years old or younger at time of revaccination.

Revaccination is also recommended for other dialysis patients, provided that

have elapsed since the first dose of vaccination

Rationale

Chronic renal failure patients are prone for pneumonia. More than75 % patients have an adequate response to the vaccine

Pneumococcal vaccine is well tolerated with only minor side effects such as pain, erythema, itching and burning at site of injection

In healthy person antibody titer remain elevated for 5 years and decrease to pre vaccination level after 10 years. But in chronic renal failure patients, a rapid decline occurs in 6 months to 5 years after vaccination.

Influenza vaccine

- Influenza vaccine should be given annually before the beginning of the influenza season for persons 6 months of age or older on dialysis.
- House hold workers and health care workers should also be vaccinated annually to decrease the transmission to high risk patients

- **Intramuscular**
  < 9 years of age – 2 doses of influenza vaccine is administered at least 1 month apart.
  9-12 years age; one dose of split virus vaccine should be given
  >12 years age; one dose of whole virus or split virus vaccine should be given

Rationale

1. Dialysis patients are at increased risk of influenza related mortality.

2. No systemic reactions have been reported following influenza vaccination in dialysis patients

Live attenuated vaccines

- Live vaccines are usually contraindicated in immunocompromised patients due to risk of vaccine induced infections
- However; studies in CRF patients have not shown any adverse reactions in few studies.
- However, due to theoretical risk of poliomyelitis, oral polio vaccine is not recommended

Measles, mumps and rubella vaccine (MMR vaccine)

- MMR vaccine should be given to all children including those on dialysis between 12 and 15 months of age with a booster dose between 4-6 years of age

Use of inactivated vaccine and toxoids in dialysis

- Haemophilus influenza Type B conjugate vaccine (Hib)
- Diphtheria and tetanus toxoids and pertussis vaccine

Hepatitis A vaccine

- Both children and adult should receive 2 doses of vaccine, intramuscularly

HBV Vaccination

it is recommended that for uremic patients, a four-dose schedule (40 ug/dose given at 0, 1, 2 and 6 months)

Charest AF, McDougall J, Goldstein MB. A randomized comparison of intradermal and intramuscular vaccination against hepatitis B virus in incident chronic hemodialysis patients. Am J Kidney Dis 2000; 36:976-982.

Chronic Hepatitis B is a Silent Threat

- Half of all people with chronic hepatitis B show no symptoms[1]
- People who have the hepatitis B virus may infect others without knowing it
- People often find out they have the hepatitis B virus after they get really sick, when it's usually too late or difficult to treat the infection
- There is no cure, but there are effective treatments available

[1] Centers for Disease Control and Prevention. Hepatitis B. Available at: http://www.cdc.gov/communication/tips/hep-b.htm. Accessed May 21, 2004.

- Chronic hepatitis B is one of the top 10 causes of death worldwide[1]
- The hepatitis B virus is 100 times more infectious than HIV[2]

[1] Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures.*J Viral Hepatitis.* 2004;11:97-107.

[2] Hepatitis B Foundation. Hep B Statistics. Available at: http://www.hepb.org/hepb/statistics.htm. Accessed December 29, 2009.

HBsAg has been detected on various environmental surfaces, such as clamps, scissors, doorknobs and dialysis machine control knobs, in dialysis centers with HBsAg-positive patients

patients on peritoneal dialysis

have a lower prevalence of HBV infection compared with hemodialysis patients

How Hepatitis B is NOT Spread

- It is NOT spread from hugging, holding hands, sharing food, breastfeeding, kissing, or living with an infected person

Epidimiology

The hepatitis B surface antigen (HBsAg) positivity rate in dialysis patients varies among different localities and correlates with the endemicity in the general population of the region.

HBsAg positivity rates among dialysis patients are reported to be 0.9% in the USA, 1.6% in Japan, 10.0% in Brazil, 10.0% in Hong Kong, 11.8% in Saudi Arabia and 16.8% in Taiwan

Tokars JI, Finelli L, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2001. Semin. Dial.2004; 17: 310–19.

Oguchi H, Miyasaka M, Tokunaga S et al.Hepatitis virus infection (HBV and HCV) in eleven Japanese hemodialysis units. Clin. Nephrol.1992; 38: 36–43

Immunologic Markers of HBV Infection

	HBsAg	HBeAg	HBVDNA	Anti HBc IgM	Anti HBc IgG	Anti HBe	Anti HBs	ALAT
Acute Virus B Hepatitis	+	+	+	+	Ø	Ø	Ø	
Chronic HBeAg pos. Hepatitis	+	+	+	Ø	+	Ø	Ø	
Chronic HBeAg neg. Hepatitis	+	Ø	+	Ø	+	+	Ø	
Chronic HBeAg neg. HBV Infection (Carrier)	+	Ø	Low or negative	Ø	+	+	Ø	normal
Occult Virus B Hepatitis	Ø	Ø	+	Ø	+	+	+	normal
Hepatitis Recovery	Ø	Ø	Ø	Ø	+	+	+	normal
Vaccination	Ø	Ø	Ø	Ø	Ø	Ø	+	normal

Patients on maintainence haemodialysis and chronic HBsAg carriage rarely develop symptoms of hepatitis, are anicteric and have mild elevations of hepatic transaminase levels but silent hepatocellular injury continues.

Fabrizi F, Lunghi G, Martin P. Hepatitis B virus infection in hemodialysis: recent discoveries. J Nephrol 2002; 15: 463-8.
Elghannam DM, Aly RM, Goda EF, Eltoraby EE, Farag RE. Clinical significance of antibody to hepatitis B core antigen in multitransfused hemodialysis patients. Asian J Transfus Sci 2009; 3: 14-7.

The transaminase levels are usually depressed in patients undergoing maintainence haemodialysis, 'normal' values of these enzymes may be indicative of a pathological state.

Lopes EP, Sette LH, Sette JB, Luna CF, Andrade AM, Moraes M, et al. Serum alanine aminotransferase levels, hematocrit rate and body weight correlations before and after hemodialysis session. Clinics (Sao Paulo) 2009; 64: 941-5.

level of HBV DNA is usually low among uraemic patients undergoing regular haemodialysis

Tseng GY, Lin HJ, Fang CT, Cheng YT, Huang CH, Tseng GC, et al. Hemodialysis reduces the viral load in uremic patients with chronic hepatitis B infection. Ren Fail 2008; 30: 1000-5.

liver biopsy

the only definitive and reliable means to establish the activity of liver disease in dialysis patients

recommended before starting antiviral therapy and undergoing kidney transplantation

Elghannam DM, Aly RM, Goda EF, Eltoraby EE, Farag RE. Clinical significance of antibody to hepatitis B core antigen in multitransfused hemodialysis patients. Asian J Transfus Sci 2009; 3: 14-7.

OCCULT HBV

HBV DNA detection in serum or in the liver by sensitive diagnostic tests in HBsAg-negative patients with or without serologic markers of previous viral exposure

Scheiblauer H, Soboll H, Nick S (2006) Evaluation of 17 CEmarked HBsAg assays with respect to clinical sensitivity, analytical sensitivity, and hepatitis B virus mutant detection. J Med Virol 78 Suppl 1: S66-70

Studies of donors who transmit post transfusion hepatitis.

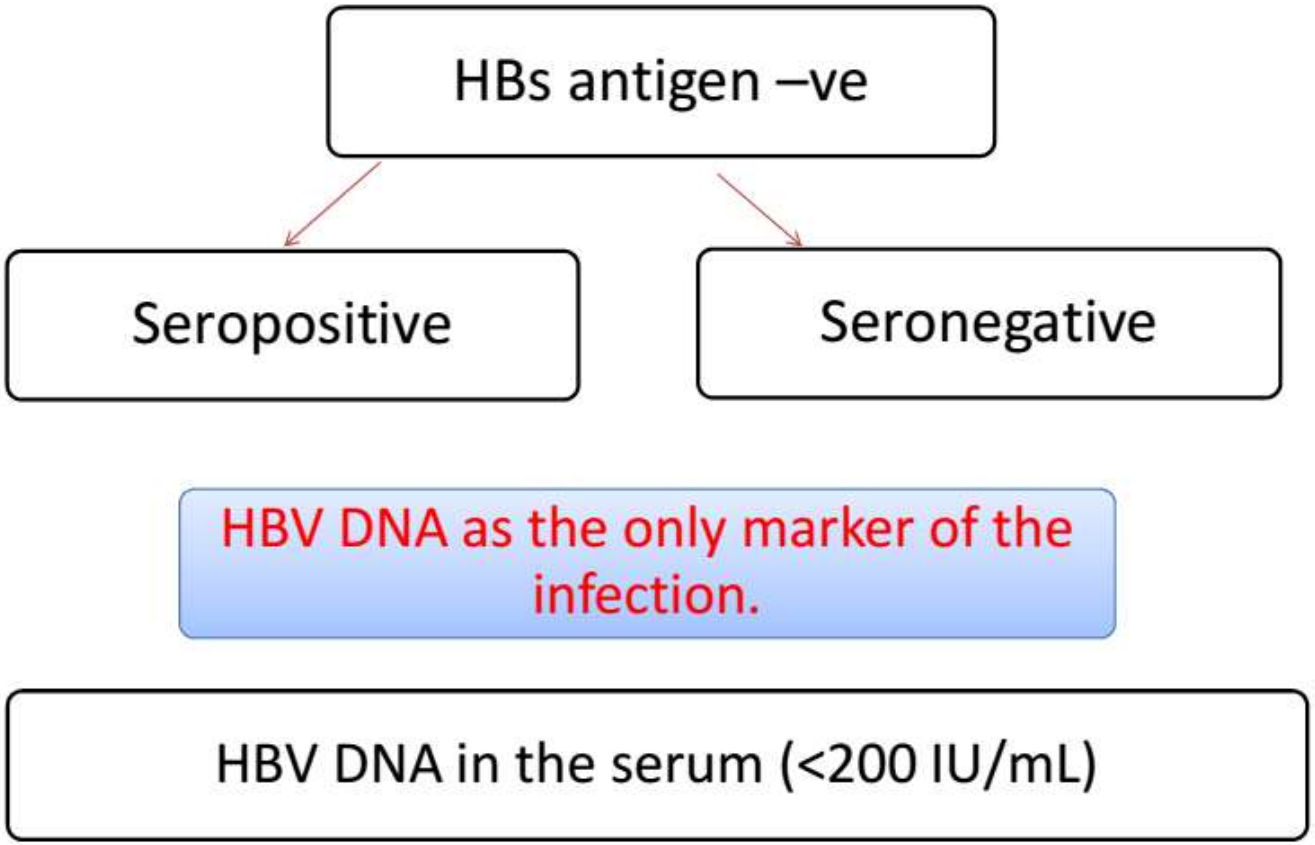
Tabor E, Hoofnagle JH, Smallwood LA, Drucker JA, PinedaTamondong GC, et al. (1979)

OBI prevalence seems to be higher among subjects at high risk for HBV infection and with liver disease

Alavian SM, Bagheri-Lankarani K, Mahdavi-Mazdeh M, Nourozi S (2008) Hepatitis B and C in dialysis units in Iran: changing the epidemiology. Hemodial Int 12: 378-382

OBI is the major cause of post transfusion hepatitis B in western countries and in countries like India and Taiwan, with higher risk of transmission than for HCV or HIV

F. A. M. Regan, P. Hewitt, J. A. J. Barbara, and M. Contreras, "Prospective investigation of transfusion transmitted infection in recipients of over 20,000 units of blood," British Medical Journal, vol. 320, no. 7232, pp. 403–406, 2000


HBs antigen –ve
Seropositive
Seronegative
HBV DNA as the only marker of the infection.
HBV DNA in the serum (<200 IU/mL)

- OHB patients on hemodialysis has ranged from 0 to 20%

- Fabrizi F, Messa PG, Lunghi G, Aucella F, Bisegna S, et al. (2005) Occult hepatitis B virus infection in dialysis patients: a multicentre survey. Aliment Pharmacol Ther 21: 1341 1347.

Prevalence of Occult Hepatitis B Virus Infection in Hemodialysis Patients From Egypt With or Without Hepatitis C Virus Infection

Mona A. Abu El Makarem [1*], Mohammed Abdel Hamid [2], Ashraf Abdel Aleem [1], Ahmed Ali [1], Mohammed Shatat [1], Douaa Sayed [3], Ali Deaf [1], Lamia Hamdy [4], Effat A. Tony [5]

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[4] Department of clinical pathology, Medical school, Minia University, Minia, Egypt
[5] Department of Internal Medicine and Nephrology, Assuit University, Asyut, Minia, Egypt

Occult hepatitis B virus infection in a cohort of Egyptian chronic hemodialysis patients.

2012

Authors Elgohry, I [2], Elbanna A [3], Hashad D [4]

Journal Clinical laboratory

Occult Hepatitis B among Patients under Hemodialysis at Mansoura University Hospitals: Prevalence and Risk Factors

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Rec date: Feb 18, 2014 **Acc date:** April 22, 2014 **Pub Date:** April 25, 2014

Occult hepatitis B virus infection among chronic hemodialysis patients in Alexandria, Egypt

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Occult HBV infection status among chronic hepatitis C and hemodialysis patients in Northeastern Egypt: regional and national overview

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[1]. Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt. [2]. Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt. [3]. Department of Microbiology and Immunology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt. [4]. Department of Microbiology and Immunology, Faculty of Medicine, Jazan University, Jazan, Kingdom of Saudi Arabia. [5]. Department of Medical Biochemistry, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

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http://dx.doi.org/10.1590/0037-8682-0037-2015

4.1%Upper Egypt

26.8%North Egypt (ALEX)

18% Mansoura

32% North Egypt (ALEX)

1.8 %The Suez Canal region

Treat or Not

Isolate or Not

ELISA Enough or Not

Vaccine

Adult Immunization Schedule – 2015, By Medical Indications

Figure 2. Vaccines that might be indicated for adults based on medical and other indications[1]

VACCINE ▼ INDICATION ►	Pregnancy	Immuno-compromising conditions (excluding human immunodeficiency virus [HIV])[4,6,7,8,11]	HIV infection CD4+ T lymphocyte count[4,6,7,8,11]: < 200 cells/μL	HIV infection CD4+ T lymphocyte count[4,6,7,8,11]: ≥ 200 cells/μL	Men who have sex with men (MSM)	Kidney failure, end-stage renal disease, receipt of hemodialysis	Heart disease, chronic lung disease, chronic alcoholism	Asplenia (including elective splenectomy and persistent complement component deficiencies)[8,12]	Chronic liver disease	Diabetes	Healthcare personnel
Influenza*[,2]	1 dose IIV annually				1 dose IIV or LAIV annually	1 dose IIV annually					1 dose IIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap)*[,3]	1 dose Tdap each pregnancy	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs									
Varicella*[,4]	Contraindicated			2 doses							
Human papillomavirus (HPV) Female*[,5]		3 doses through age 26 yrs				3 doses through age 26 yrs					
Human papillomavirus (HPV) Male*[,5]		3 doses through age 26 yrs				3 doses through age 21 yrs					
Zoster[6]	Contraindicated				1 dose						
Measles, mumps, rubella (MMR)*[,7]	Contraindicated			1 or 2 doses							
Pneumococcal 13-valent conjugate (PCV13)*[,8]		1 dose									
Pneumococcal polysaccharide (PPSV23)[8]		1 or 2 doses									
Meningococcal*[,9]	1 or more doses										
Hepatitis A*[,10]	2 doses										
Hepatitis B*[,11]	3 doses										
Haemophilus influenzae type b (Hib)*[,12]	post-HSCT recipients only	1 or 3 doses									

*Covered by the Vaccine Injury Compensation Program

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly recommended for adults ages 19 years and older, as of February 1, 2015. For all vaccines being recommended on the Adult Immunization Schedule: a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/hcp/acip-recs/index.html). Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

http://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html

So tell me,
this physician of whom
you were just speaking,
Is he a money maker,
an earner of fees,
or a healer of the sick?

Plato, *The Republic*